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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 10/006,818
Filing Date: December 06, 2001
Appellant(s): BAKER ET AL.

Anna L. Barry
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 22 November 2005 appealing from the Office action mailed 03 January 2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner, which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

There exist two related patent applications, (1) U.S. Serial No. 10/015,869, filed December 11, 2001 (containing claims directed to polynucleotides encoding PR01293 polypeptides, has been allowed on 29 December 2005), and (2) U.S. Serial No. 10/006,063, filed December 6, 2001 (containing claims directed to the PR01293 polypeptides), also being appealed.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be reviewed at Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

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(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Pennica et al., 1998, PNAS USA 95:14717-14722.

Hu et al., 2003, Journal of Proteome Research 2:405-412.

Konopka et al. 1986 , PNAS USA 83:4049-4052.

Haynes et al., 1998, Electrophoresis, 19:1862-1871.

Chen et al., 2002, Molecular and Cellular Proteomics 1 :304-313.

Gygi et al., 1999, Mol. Cell. Biol. 19:1720-1730.

Lian et al., 2001, Blood 98:513-524.

Fessler et al., 2002, J. Biol. Chem. 277:31291-31302.

Greenbaum et al. (2003, Genome Biology 4:117.1-117.8)

(9a) NEW GROUND OF REJECTION

The following ground of rejection is applicable to the appealed claims:

Claims 28-32 are rejected under 35 U.S.C. 101. Although this rejection is set forth in the prior Office Actions mailed on 19 August 2004 and 03 January 2004, it is considered a new ground of rejection, because of the reliance of eight new references, (Pennica et al., Konopka et al., Haynes et al., Chen et al, Gygi et al, , Lian et al., Fessler et al., and Greenbaum et al.) to support the rejection.

Claim Rejections - 35 U.S.C. §101:

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Claims 28-32 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The claims are directed to an isolated antibody that specifically binds to the polypeptide whose amino acid sequence is set forth in SEQ ID NO:77, which is a monoclonal antibody, which is humanized, which is labeled and which is a fragment. The specification teaches that the polypeptide of SEQ ID NO:77, also known as "PRO1293", is a novel polypeptide that has homology to an immunoglobulin heavy chain variable region protein, (page 79, lines 36-40).

However the specification fails to disclose the percent homology shared between the claimed polypeptide and said region, any antigenic properties for the claimed polypeptide; which class of immunoglobulins it belongs to; or any biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner; or any other specific feature associated with the PRO1293 polypeptide. Without any information as to the specific properties of PRO1293, the mere disclosure that it has homology to an immunoglobulin heavy chain variable region is not sufficient to impart a well-established utility to the claimed polypeptides. The specification contains numerous asserted utilities for the PRO1293 polypeptide, including use as molecular weight markers, therapeutic agents, and for the production of antibodies. None of these asserted utilities is specific for the disclosed PRO1293 polypeptide, as each of the aforementioned utilities could be asserted for any naturally occurring polypeptide, and further, as none of the asserted utilities requires any feature or activity that is specific to

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the disclosed the PRO1293 polypeptide. The specification asserts that antibodies that bind to the PRO1293 polypeptide would be expected to have utility in cancer therapy, (page 507, lines 10-13). However, the specification does not establish a link between the polypeptide of SEQ ID NO:77 and any cancer. Accordingly, antibodies that bind to the polypeptide of SEQ ID NO:77 would not be useful in cancer therapy.

The specification discloses that the gene encoding PRO1293 was amplified in one primary lung tumor (HF-000840) two colon tumors, (HF:000539, and HF-000795), (see page Example 143 on page 494 and 503, column 1). The specification asserts that gene amplification is associated with over-expression of the gene product, indicating that antagonists (e.g antibodies) directed against the PRO1293 polypeptide would be expected to have utility in cancer therapy, (page 507, lines 5-13). The specification also generally asserts that the polypeptides and antibodies that bind them are useful as diagnostics for cancer. However, the instant specification does not demonstrate that the PRO1293 polypeptide is actually overly expressed in any of the cancers mentioned. Appellants have not shown that there is a relationship between DNA amplification in said cancers and increased amounts of corresponding mRNA or protein. Therefore, antibodies that bind to the PRO1293 polypeptide would not be useful in diagnosing said cancers or as therapeutic targets for said cancers. Although the data in the instant specification shows that gene copy number is increased in certain tumor tissue samples, it does not necessarily follow that an increase in gene copy (DNA) number results in increased gene expression (mRNA) and increased protein expression, such that the polypeptide of SEQ ID NO:77, or variants of the polypeptide of

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SEQ ID NO:77, would be useful diagnostically or as target for cancer drug development.

In order for PRO1293 polypeptides to be overexpressed in lung or colon tumors, amplified genomic DNA would have to correlate with amplified mRNA, which in turn would have to correlate with amplified polypeptide levels. The art discloses that such correlations cannot be presumed. Regarding the correlation between genomic DNA amplification and increased mRNA expression, see Pennica et al. (1998, PNAS USA 95:14717-14722), who disclose that:

“An analysis of WISP-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of WISP-3 RNA was seen in the absence of DNA amplification. In contrast, WISP-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient.”

See p. 14722, second paragraph of left column; pp. 14720-14721, “Amplification and Aberrant Expression of WISPs in Human Colon Tumors.” See also Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that “Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template” (see abstract). Even if increased mRNA levels could be established for PRO1293, it does not follow that polypeptide levels would also be amplified. Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al. clearly state that “the use of mRNA expression patterns by themselves, however, is insufficient for

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understanding the expression of protein products” (p. 304) and “it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples” (pp. 311-312). Also, Hu et al. (2003, *Journal of Proteome Research* 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

The art also shows that mRNA (transcript) levels do not correlate with polypeptide levels in normal tissues. See Haynes et al. (1998, *Electrophoresis* 19:1862-1871), who studied more than 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between protein and transcript level. For some genes, equivalent mRNA levels translated into protein abundances, which varied more than 50-fold. Haynes et al. concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Gygi et al. (1999, *Mol. Cell. Biol.* 19:1720-1730) conducted a similar study with over 150 proteins. They concluded that:

“the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data. Indeed, for some genes, while the mRNA levels were of the same value the protein levels varied by more than 20-fold. Conversely, invariant steady-state levels of certain proteins were

observed with respective mRNA transcript levels that varied by as much as 30-fold. Our results clearly delineate the technical boundaries of current approaches for quantitative analysis of protein expression and reveal that simple deduction from mRNA transcript analysis is insufficient" (Abstract).

Lian et al. (2001, Blood 98:513-524) show a similar lack of correlation in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al. (2002, J. Biol. Chem. 277:31291-31302) who found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract). Greenbaum et al. (2003, Genome Biology 4:117.1-117.8) cautions against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, most notably in human cancers and yeast cells. And, for the most part, they have reported only minimal and/or limited correlations. The reference further teaches (page 117.4, 2nd column) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well

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defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their in vivo half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 117.6, page 2nd column) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood.

Therefore, data pertaining to PRO1293 genomic DNA do not indicate anything significant regarding the PRO1293 polypeptides or antibodies that bind it. The data do not support the specification's assertion that PRO1293 polypeptides and/or antibodies that bind it, can be used as cancer diagnostic agents or as therapeutic drug development targets. Significant further research would have been required of the skilled artisan to reasonably confirm that PRO1293 polypeptide is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic agent or therapeutic drug development target, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO1293 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO1293 polypeptides or antibodies that bind them, as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides. See *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific

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benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

9b. Claims 28-32 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Accordingly, since the instant specification provides no information regarding the physiological significance, functional characteristics or any conditions that involve the polypeptide of SEQ ID NO:77, (PRO1293 polypeptide), the PRO1293 polypeptide and antibodies that bind it, lack specific and substantial asserted utility or a well established utility

(10a) Response to Arguments:

At pages 7-10 of the Brief, Appellant reviews the legal standard for utility, with which the Examiner takes no issue.

At pages 10-12 of the Brief, Appellant argues that the data in Example 143 (starting at p. 494 of the specification) describes results of a gene amplification assay. Appellant characterizes the assay as using a well-known and routinely employed PCR assay that is capable of quantitatively measuring the level of gene amplification in a sample. Appellant asserts that gene amplification is an essential mechanism for oncogene activation. Appellant reviews how the assay was performed, and reports that the gene encoding PRO1293 was significantly amplified (2.189-fold to 5.028 -fold) in

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one lung tumor sample and two colon tumor samples. Appellant asserts that Example 143 provides utility for the claimed antibodies in cancer diagnostics. This has been fully considered but is not found to be persuasive. First, it is important to note that the gene encoding PRO1293 has not been found to be amplified in any of the 19 lung tumor samples, or any of the 17 colon tumor samples listed on table 7 of the instant specification (see page 499). The specification discloses that the gene encoding PRO1293 was amplified in one primary lung tumor HF-000840, and two colon tumor centers: HF:000539 and HF-000795, (see page 507, lines 5-12). The specification does not list said tumors on table 7, on page 499, which discloses the profiles of 19 lung and 17 colon primary tumors. Table 7, lists the T, N and M stages for the listed tumor samples. However, the specification does not disclose any information for the one lung sample and the two colon tumor samples that the gene encoding the PRO1293 is allegedly amplified. For example, what stage tumor have these samples been isolated from or what type of lung or colon tumors are they. Furthermore, the PRO1293 is amplified in only 3 out of 52 tested samples, (see table 8). Also, matched tissue samples were not used for controls. Rather, the control DNA appears to have been isolated from blood (bottom of p. 500). The art uses matched tissue samples as the standard in such cases (see Pennica et al.). Given these details, one skilled in the art would not conclude that the gene encoding PRO1293 would be useful as a cancer diagnostic or a target for cancer drug development, but would rather view the data as preliminary results. Moreover, the data pertaining to gene amplification do not convey utility to the polypeptide of SEQ ID NO:77 or antibodies that bind it, since a small

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amplification in genomic DNA is shown in the art to fail to correlate with a corresponding increase in mRNA and polypeptide levels (see Pennica et al, Hu et al and Konopka et al).

From pages 11-12 of the Brief, Appellant refers to the declaration of Dr. Goddard, submitted under 37 C.F.R. § 1.132 on 19 August 2004. Appellant quotes from p. 3 of the declaration as giving an expert opinion that a 2-fold increase in gene copy number in a tumor sample relative to a non-tumor sample is significant and useful. Appellant concludes that one skilled in the art would consider the 2.189-5.028 -fold amplification of the gene encoding PRO1293 in one lung tumor and two colon tumors is significant and credible based upon the facts in the Goddard declaration. This has been fully considered but is not found to be persuasive. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not a 2.189-5.028 -fold amplification of the gene encoding PRO1293 in one lung tumor and two colon tumors, is significant and credible. Credibility has never been questioned. However, the significance can be questioned since 49 out of 52 tested tumor samples did not show an amplification of the gene

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encoding PRO1293, and the control used was not a matched non-tumor lung sample but rather was a pooled DNA sample from blood of healthy subjects. The art uses matched tissue samples (see Pennica et al.). Moreover, the expert (Dr. Goddard) has interest in the outcome of the case since he is listed as an inventor and is employed by the assignee. Finally, the expert refers to six publications as factual support for the conclusions in the declaration. However, none of Higuchi et al., Livak et al., Heid et al., Pennica et al., Pitti et al., or Bieche et al., appear to indicate that an approximately 2-5 fold amplification of genomic DNA is significant in tumors. The Goddard declaration evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO1293 gene has not been associated with tumor formation, the development of cancer, the progression of cancer, the prediction of cancer, or the recovery from cancer during treatment. The specification merely demonstrates that the PRO1293 genomic DNA was amplified in some cancers, to a minor degree (about 2-5 fold), relative to normal blood DNA. No mutation or translocation of PRO1293 has been associated with any type of cancer versus normal tissue. It is not known whether PRO1293 is amplified in corresponding normal tissues, and what the relative levels of amplification are. In the absence of any of the above information, all that the specification does is indicate that the DNA encoding PRO1293 may be amplified in a variety of samples and invites the artisan to determine the significance of this increase. The specification presents a mere invitation to experiment. Based on consideration of the evidence as a whole, the rejection is proper.

At pages 12-13 of the Brief, Appellant argues that there is an overwhelming evidence gene amplification data disclosed in the specification that the PRO1293 is amplified in certain lung and colon tumors. Appellants further submit that it is well known in the art that if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. This has been fully considered but is not found to be persuasive. Firstly, the PRO1293 gene is amplified in only 3 samples out of 52 samples that were tested. Secondly, there is no control for non-cancerous lung or colon tissue, and thus the relevance of the data in the specification is not clear. Furthermore, there is no disclosure of a correlation of amplification with tumor formation, progression, severity, etc., all of which would speak to prognosis.

At pages 12-13 of the Brief, Appellant argues that there is no legal requirement to establish that gene amplification “necessarily” results in increased expression at the mRNA and polypeptide levels or that protein levels can be “accurately predicted”. Appellant submits that the evidentiary standard to be used in *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Appellant contends that the Examiner must establish that “it is more likely than not: that one of ordinary skill in the art would doubt the truth of the statement of utility. This has been fully considered. Appellant is correct in that the totality evidence has to be considered in examining patent application. In the instant case, neither the PRO1293 gene nor the PRO1293 polypeptide has been associated with tumor formation or the development of cancer, nor has either been shown to be predictive of such. Similarly, the PRO12931 gene has not been shown to be useful to track the

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efficacy of cancer therapy. The specification merely demonstrates that the PRO1293 genomic DNA may be amplified in some cancers, to a minor degree (about 2-5 fold) compared to normal DNA from blood. No mutation or translocation of PRO1293 has been associated with any type of cancer versus normal tissue. It is not known whether PRO1293 is amplified in corresponding normal tissues, and what the relative levels of amplification are. In the absence of any of the above information, all that the specification does is present evidence that the DNA encoding PRO1293 may be amplified in a variety of samples and invites the artisan to determine the significance of this increase. Therefore, it remains that, as evidenced by Pennica et al., Konopka et al., Haynes et al., Chen et al., Gygi et al., Lian et al. and Fessler et al., the issue is simply not predictable, and the specification presents a mere invitation to experiment. Based on consideration of the evidence as a whole, the rejection is proper.

From pages 13-15 of the Brief, Appellant criticizes the Hu et al. reference. Specifically, Appellant criticizes Hu et al. for being based upon a statistical analysis of information from published literature rather than from experimental data. Appellant characterizes Hu et al. as being limited to estrogen-receptor-positive breast tumor only. Appellant criticizes the types of statistical tests performed by Hu et al. Appellant concludes that, based on the nature of the statistical analysis performed in Hu et al., and the fact that Hu et al. only analyzed one class of genes, the conclusions drawn by the examiner are not reliably supported. This has been fully considered but is not found to be persuasive. The asserted utility for the claimed polypeptides is based on a sequence of presumptions. First, it is presumed that gene amplification predicts

increased mRNA production. Second, it is presumed that increased mRNA production leads to increased protein production. Hu et al. is directly on point by showing that the second presumption is incorrect when designating proteins as diagnostic markers for cancer. Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). The instant specification does not disclose that PRO1293 mRNA levels are expressed at 10-fold or higher levels compared with normal, matched tissue samples. Therefore, based on Hu et al., the skilled artisan would not reasonably expect that PRO1293 protein can be used as a cancer diagnostic. Furthermore, Hanna et al. show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. The instant specification does not provide additional information regarding whether or not PRO1293 mRNA or polypeptide is overexpressed in lung or colon and thus the skilled artisan would need to perform additional experiments to reasonably confirm such. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial. Regarding Appellant's criticism of Hu et al.'s statistical analysis, Appellant

is holding Hu et al. to a higher standard than their own specification, which does not provide proper statistical analysis such as reproducibility, standard error rates, etc.

Regarding Appellant's criticism of Hu et al. as being limited to a specific type of breast tumor, Hu et al. is cited as one of several pieces of evidence that gene amplification in a tumor does not correlate with mRNA overproduction or protein overproduction. When viewed with the evidence of record as a whole, there is no correlation between gene amplification, mRNA levels and protein levels. In view of the totality of the evidence, including the declarations submitted under 37 CFR 1.132 and the publications of record, the instant utility rejection is appropriate.

At pages 15-16 of the Brief, Appellant refers to Orntoft et al., Hyman et al., and Pollack et al. as evidence supporting the assertion that gene amplification more likely than not correlates with increased polypeptide levels. Appellant characterizes Orntoft et al. as studying transcript levels of 5600 genes in malignant bladder cancers, many of which were linked to the gain or loss of chromosomal material and found that in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Appellant characterizes Hyman et al. as comparing DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, and found that there was evidence of a prominent global influence of copy number changes on gene expression levels. Appellant characterizes Pollack et al. as profiling DNA copy number alteration across 6691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines, and found that on average, a 2-fold change in DNA copy number was associated

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with a corresponding 1.5-fold increase in mRNA levels. Appellant concludes that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels. This has been fully considered but is not found to be persuasive. Orntoft et al. (Molecular and Cellular Proteomics 1:37-45, 2002) could only compare the levels of about 40 well-resolved and focused abundant proteins." (See abstract.) It would appear that Appellants have provided no fact or evidence concerning a correlation between the specification's disclosure of low levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded protein. Hyman (Cancer Research 62:6240-6245) found 44% of highly amplified genes showed overexpression at the mRNA level, and 10.5% of highly overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO1293 would be correlated with elevated levels of mRNA, much less protein. Hyman does not examine protein expression. Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification. None of the three references are directed to gene amplification, mRNA levels, or polypeptide levels in lung or colon cancer.

At pages 17-18 of the Brief, Appellant refers to the declaration of Dr. Polakis, submitted under 37 C.F.R. § 1.132 with the response filed 19 August 2004. Appellant

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characterizes the declaration as setting forth Dr. Polakis' experience with microarray analysis wherein approximately 200 gene transcripts present in human tumor cells were found to be at significantly higher levels than in corresponding normal human cells. The declaration goes on to state that antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels compared. The declaration states that in approximately 80% of the cases, the researchers found that increased levels of RNA correlated with changes in the level of protein. Appellant concludes that all of the submitted evidence supports Appellant's position that it is more likely than not that increased gene amplification levels predict increased mRNA and increased protein levels, thus meeting the utility standards. This has been fully considered but is not found to be persuasive. As discussed above, in assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. (1) In the instant case, the nature of the fact sought to be established is whether or not gene amplification is predictive of increased mRNA levels and, in turn, increased protein levels. Dr. Polakis declares that 80% of approximately 200 instances of elevated mRNA levels were found to correlate with increased protein levels. (2) It is important to note that the instant specification only discloses gene amplification data for PRO1293 (i.e., data regarding amplification of PRO1293 genomic DNA), and does not disclose any information regarding PRO1293 mRNA levels. Furthermore, there is strong opposing evidence showing that gene

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amplification is not predictive of increased mRNA levels in normal and cancerous tissues and, in turn, that increased mRNA levels are frequently not predictive of increased polypeptide levels. See, e.g., Pennica et al., Hu et al. (who reviewed 2286 genes reported in the literature to be associates with breast cancer). (3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Polakis is employed by the assignee. (4) Finally, Dr. Polakis refers to facts; however, the data is not included in the declaration so that the examiner could not independently evaluate them. For example, how many of the tumors were lung tumors? How highly amplified were the genes that correlated with increased polypeptide levels?

At page 17 of the Brief, Appellant notes that the sale of gene expression chips to measure mRNA levels is a highly successful business. Appellant concludes that the research community believes that the information obtained from the chips is useful (i.e., that it is more likely than not that the results are informative of protein levels). This has been fully considered but is not found to be persuasive. Evidence of commercial success has no bearing on the issue of utility. The research community could just as easily be interested in the gene chips as a way of providing preliminary results, which would then be followed up with actual testing of protein levels.

From pages 17-19 of the Brief, Appellant addresses the comments made in the final rejection regarding the Orntoft et al., Hyman et al., and Pollack et al. references. Appellant argues that Orntoft et al. studied 1800 genes that yielded an increase or decrease in mRNA expression in two invasive tumors compared to non-invasive papillomas (also tumors), and then mapped them to chromosomal locations. Appellant

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argues that the chromosomal locations had already been analyzed for amplification via CGH. Appellant argues that Orntoft et al. found that in general areas with strong gain of chromosomal material contained a cluster of genes having increased mRNA expression. Appellant quotes from Orntoft et al. as stating that a highly significant correlation was observed between the level of CGH ratio change (DNA copy number) and alteration detected by arrays (mRNA levels). Appellant argues that Orntoft et al. studied mRNA relation to protein levels and found a highly significant correlation. Appellant concludes that Orntoft et al. supports Appellant's position that proteins expressed by genes that are amplified in tumors are useful as cancer markers. Appellant also argues that there is no clear relevance of the examiner's concern that PRO1293 has not been disclosed as being part of a gene cluster. This has been fully considered but is not found to be persuasive. As discussed above, Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). Orntoft et al.'s findings could only be extended to other genes in such clusters. This analysis was not done for PRO1293 in the instant specification, and so it is not clear whether or not PRO1293 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the findings of Orntoft et al. cannot be extended to PRO1293. Also, Orntoft et al. compared genes from non-invasive transitional cell carcinomas to genes from invasive transitional cell carcinomas. There was no comparison between genes in cancerous versus non-cancerous tissue. Thus, Orntoft et al. did not find any cancer markers. Furthermore, Orntoft et al. could only compare the levels of about 40 well-resolved and focused abundant proteins. (See

abstract.) Appellant has provided no fact or evidence concerning a correlation between the specification's disclosure of low levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded protein. Finally, Orntoft et al. did not study lung or colon cancer.

At pages 19-20, Appellant argues that the examiner has mischaracterized the methods used by Hyman et al. and Pollack et al. Appellant urges that these papers did not use traditional CGH, but rather did gene-by-gene analysis across all chromosomes. Appellant characterizes Hyman et al. as studying 13,824 clones for gene expression and gene copy number in 14 breast cancer cell lines. Appellant quotes from Hyman et al. regarding their finding that up to 44% of the highly amplified genes were overexpressed compared with only 6% for genes with normal copy number. Appellant further quotes from Hyman et al. regarding the cDNA/microarray technique enables the direct correlation of copy number and expression data on a gene-by-gene basis throughout the genome. Appellant concludes that Hyman et al. performed an analysis on a gene-by-gene basis, and clearly shows that it is more likely than not that a gene which is amplified in tumor cells will have increased gene expression. This has been fully considered but is not found to be persuasive. As discussed above, Hyman et al. found 44% (less than half) of highly amplified genes showed overexpression at the mRNA level, and 10.5% of highly overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. This is direct evidence that it is "more likely than not" that gene amplification does not correlate with increased mRNA expression. Further, the article at page 6244 states that of the

12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO1293 would be correlated with elevated levels of mRNA, much less protein. Also, Hyman et al. did not evaluate lung cancer.

At pages 19-20 of the Brief, Appellant characterizes Pollack et al. as studying DNA copy number across 6691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines. Appellant quotes from Pollack et al., saying that parallel microarrays measurements of mRNA levels reveal the remarkable degree to which variation in gene copy number contributes to variation in gene expression in tumor cells, and that genome-wide, of 117 high-level DNA amplifications, 62% are found associated with at least moderately elevated mRNA levels and 42% associated with highly elevated mRNA levels. Appellant concludes that the Pollack et al. reference constitutes evidence that it is more likely than not that a gene which is amplified in tumor cells will have increased gene expression. This has been fully considered but is not found to be persuasive. As discussed above, Pollack et al. also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification, and did not test for protein expression levels. Also, Pollack et al. did not study lung cancer.

At pages 20-22 of the Brief, Appellant comments upon the examiner's evaluation of the Polakis declaration. Specifically, Appellant argues that the Polakis declaration

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was submitted to support the position that there is a correlation between mRNA and polypeptide levels, and that the correlation between gene amplification and mRNA levels had been supported by other evidence. Appellant urges that the opinions in the Polakis declaration are all based on factual findings. Appellant cites case law concerning the examiner's requirement to consider all of the evidence of record anew, and that opinion evidence must be considered. Appellant also points to the utility guidelines as directing the examiner to accept an opinion from an expert. Appellant points to the statement in the Polakis declaration that it is Dr. Polakis' considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates with a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. Appellant concludes that the fact-based conclusions of Dr. Polakis would be considered reasonable and accurate by the skilled artisan. This has been fully considered but is not found to be persuasive. As discussed above, in assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. (1) In the instant case, the nature of the fact sought to be established is whether or not increased mRNA levels are predictive of increased polypeptide levels. (2) The art provides strong evidence that increased mRNA levels do not correlate with increased protein levels in both healthy and cancerous tissues. See Hu et al., and Pennica et al., (3) Dr. Polakis has an interest in the case since he is employed by the

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assignee. Finally, (4) while Dr. Polakis bases his findings with reference to facts, the facts are not independently provided for the examiner to draw independent conclusions. For example, it is not clear if any of the tumors were from lung or colon, or how highly amplified the genes were that correlated with polypeptide overexpression. Based on the totality of the evidence, considering it anew, it is maintained that one skilled in the art would view the instant gene amplification data as merely preliminary with regard to whether or not mRNA or protein levels of PRO341 are specifically amplified in lung tumors. Further research would have to be done in order to determine if PRO1293 mRNA and protein are amplified and, if so, whether or not the amplification is significant enough to reasonably confirm the usefulness of PRO1293 protein or antibodies that bind, as a lung or colon cancer marker. Thus, the claimed invention does not provide products or services in "currently available" to the public, and the asserted utility is not substantial.

At pages 22-23 of the Brief, Appellant argues that even if an amplified gene did not correlate with an overexpressed encoded protein, the protein would still have a credible, specific, and substantial asserted utility. Appellant points to the declaration of Dr.. Ashkenazi, submitted under 37 CFR 1.132 on 19 August 2004, as establishing that, even if the protein were not overexpressed, the simultaneous testing of gene amplification and gene product overexpression would enable more accurate tumor classification. Appellant concludes that such a situation would allow for better tumor classification and better determination of suitable therapy. Appellant argues that absence of overexpression is crucial information for a clinician, because it indicates that

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the patient should not be treated with agents that target that gene product. Appellant argues that this saves money and benefits the patients who can avoid exposure to the side effects associated with such agent. This has been fully considered but is not found to be persuasive. The specification does not disclose such further testing of gene product overexpression. Therefore, the skilled artisan would have been required to do the testing to reasonably confirm whether or not the PRO1293 polypeptide is overexpressed. In view of such requirement, the products or services based on the claimed invention are not in "currently available" form for the public. Furthermore, the specification provides no assertion that the claimed PRO1293 polypeptides are useful in tumor categorization, nor does it provide guidance regarding what treatment modalities should be selected by a physician depending upon whether or not a tumor overexpresses PRO1293. For example, neither the specification nor the prior art discloses an antagonists against PRO1293 that is useful for cancer therapy. This is also further experimentation that would have to be performed by the skilled artisan, indicating that the asserted utility is not substantial.

At page 25 of the Brief, Appellant argues that the Hanna et al. reference supports the utility of tumor categorization. Appellant characterizes Hanna et al. as disclosing that the HER-2/neu gene is amplified and/or overexpressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinomas. Appellant argues that Hanna et al. disclose that diagnosis of breast cancer includes testing for both amplification of the HER-2/neu gene and overexpression of HER-2/neu gene product. Appellant argues that even when the protein is not overexpressed, the assay relying on

both tests leads to a more accurate classification of the cancer and a more effective treatment of it. Appellant comments on the examiner's criticism of Hanna et al., stating that the examiner has misread the reference. Appellant argues that Hanna et al. disclose that gene amplification and protein overexpression are well correlated, and that only a subset of tumors show discordant results. Appellant urges that Hanna et al. support Appellant's position that it is more likely than not that gene amplification correlates with increased polypeptide expression. Appellant argues that the IHC is not used to test polypeptide expression levels empirically. Appellant argues that, rather, the screening strategy is for the selection of patients who should receive treatment with Herceptin. Appellant concludes that the purpose of measuring both protein and gene levels is not for further experimentation, but for further characterization of tumors into medically relevant categories. This has been fully considered but is not found to be persuasive. Hanna et al. clearly show that the skilled artisan does not assume that any tumor with a HER-2/neu gene amplification event also overexpressed HER-2/neu protein. It is tested empirically. The reason for the testing is irrelevant to the issue at hand. The fact remains that the instant specification does not disclose whether or not PRO1293 protein is overexpressed in any tumors. Therefore, the skilled artisan must perform further research in order to reasonably confirm whether it is or is not. The requirement for such further research indicates that the asserted utility of PRO1293 as a cancer diagnostic agent is not substantial. The specification does not assert that PRO1293 is useful as an agent to categorize tumors. However, even if it had, the specification does not disclose the expression levels of PRO1293 protein in any tumor

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samples, so that such would have to be determined through further research on the part of the skilled artisan. Thus, even the utility proposed in the Brief regarding the usefulness of PRO1293 protein in the categorization of tumors, is not substantial. Finally, there is no disclosure regarding what treatment modality should be chosen by the clinician based on whether or not PRO1293 polypeptide is overexpressed. The determination of such constitutes further experimentation, indicating that the asserted utility is not substantial.

At page 24 of the Brief, Appellant argues that the Ashkenazi declaration and the Hanna et al. reference provide evidence that, even if gene amplification were not to result in overexpression of the encoded polypeptide, analysis of the expression of the polypeptide is useful in determining the course of treatment. Appellant argues that the examiner is incorrect in asserting that such testing involves further characterization of the PRO1293 polypeptide itself. Appellant argues that such testing is for the purpose of characterizing the tumors into medically relevant categories. Appellant adds that such testing techniques were routine in the art of clinical oncology at the time of filing of the instant application. This has been fully considered but is not found to be persuasive. First, testing whether or not a polypeptide is overexpressed in a particular tumor yields information regarding the tumor and the polypeptide itself. Second, the specification does not assert that PRO1293 polypeptide is useful as a tumor categorization agent. Such is only presented in the arguments and declaration. Third, even if such were asserted in the specification as filed, the skilled artisan would still have to perform further research to reasonably confirm whether or not PRO1293 polypeptide is

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overexpressed in any tumor, since the expression levels of PRO1293 polypeptide are not disclosed in the specification. The requirement for such further research indicates that the utility is not in currently available form, i.e., it is not substantial. Finally, it is no small matter to go from information regarding protein expression levels in a tumor to designing a therapeutic regimen specific to the protein expression profile. In Hanna et al., Herceptin was discussed as a drug specific to tumors expressing HER-2/neu. Herceptin had been known prior to the publication of Hanna et al. No such drug is disclosed in the specification or in the prior art, regarding the PRO1293 polypeptide. Identifying a drug specific for PRO1293 would involve more than routine experimentation, as it would require a great amount of experimentation (e.g., screening agents for effects on PRO1293 polypeptide and on tumor), considering there is no guidance or working examples relative to such drugs in the specification or the prior art. Accordingly, since the PRO1293 polypeptide (SEQ ID NO:77) lacks a specific and substantial asserted utility or a well established utility, antibodies that binds said polypeptide also lack a specific and substantial asserted utility or a well established utility.

(9c) WITHDRAWN REJECTIONS:

The following ground of rejection is not presented for review on appeal because they have been withdrawn by the examiner.

The rejections of claims 28-32 made under U.S.C. § 102 (a) as being anticipated by Botstein et al (WO2000053751; published 14 September 2000), is withdrawn.

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Since the current application is a direct continuation of the International Application PCT/US00/04342, the subject matter defined in instant claims 28-32 is afforded an effective filing date of 18 February 2000, which is the filing date of the International Application PCT/US00/04342. Accordingly, the rejection of claims 28-32 made under U.S.C. § 102 (a) as being anticipated by Botstein et al (WO2000053751; published 14 September 2000), is withdrawn, because the effective filing date of the current application is prior to the publication date of the cited reference.

(11) Related Proceedings Appendix


No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections made under 35 U.S.C. 101/112 first paragraph should be sustained.

Respectfully submitted,

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